

REMARKS

The Amendments

Applicants have amended claims 1-3 and 19-23 to recite that the antibody and antibody fragment crystals of the present invention are characterized by  $\beta$ -sheet structural content, as indicated by a correlation spectra as compared to the soluble counterpart of said antibody, as determined by FTIR, that is between about 0.8 and about 1.0. Support for this amendment is found in the specification, e.g., on page 80, lines 20-30 and in claim 4 as originally filed.

Applicants have amended claims 62 and 64 to delete the phrase "above". In addition, applicants have amended claim 64 to replace "25" with "200". These amendments are supported on page 68, lines 26-27 and page 69, lines 1-3 of the specification.

Applicants have also added claim 79, which is directed to antibody or antibody fragment crystals produced according to the large-scale batch crystallization method according to claim 43. Support for this amendment is found in the specification, e.g., on page 67, line 23 - page 75, line 5.

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Applicants have also added claim 80. Support for this claim is found throughout Examples 1-37 as well as in original claim 8. Also added are claims 81-83, which are supported in the specification at page 58, line 15 - page 60, line 18 and in original claims 13, 15 and 16.

Applicants have also amended claim 52 to clarify that the recited polyethelene glycol (PEG) concentration is that of the crystallization buffer. Claims 53-55 have been amended to replace the term "contains" with "comprises". Claim 70 has been amended to qualify the term "fragment" with the term "antibody". Claim 75 has been amended to recite the terms "antibody fragment" and "single-chain Fv antibody fragment or an Fab antibody fragment".

Finally, in view of the amendments to claims 1-3 and 19-23, applicants have canceled claim 4.

None of the above-discussed claim amendments or additions constitutes new matter.

The Response to Office Action

Claim 52 stands rejected under 35 U.S.C. § 112, second paragraph, for lack of antecedent basis for the phrase

"polyethylene glycol (PEG) concentration". Applicants have obviated this rejection by amending the claim to reflect that the polyethylene glycol (PEG) concentration is that of the crystallization buffer.

Claims 1, 4-6, 9-11, 21-25, 31 and 33 stand rejected under 35 U.S.C. § 102(b), as being "anticipated by" Harris et al. (Proteins: Structure Funct. Genet. 1995; "Harris"). The Examiner contends that Harris discloses the crystallization of intact monoclonal antibodies. The Examiner also asserts that the antibodies disclosed in Harris are inherently characterized by the properties of the antibody and antibody fragment crystals of the present invention, i.e., the  $\beta$ -sheet structural content and the increased half-life over its soluble counterpart. Applicants disagree.

As noted by the Examiner, any protein can be characterized by its structural content, whether by its  $\beta$ -sheet structural content or otherwise. The extent of  $\beta$ -sheet structural content, however, varies widely from protein to protein. The measure of the structural content of a crystallized protein as compared to its soluble protein counterpart is a measure of how intact the structure of the

protein remains after crystallization. As recited in amended claims 1-3 and 19-23, the antibody and antibody fragment crystals of the present invention are characterized by "the  $\beta$ -sheet structural content of the antibody or fragment, as indicated by a correlation spectra as compared to the soluble counterpart of said antibody or antibody fragment, determined by FTIR, that is between about 0.8 and about 1.0". The FTIR analysis discussed in the specification (page 80, line 20 - page 81, line 2 and Example 58) and recited in amended claims 1-3 and 19-23, signifies that the crystals of the present invention maintain a high degree of the structure that characterizes them in their soluble state. This, in turn, means that these crystals retain a high degree of their functionality and can therefore be effectively used in a variety of applications, including therapeutic applications.

In contrast, the crystallized antibodies of Harris were generated for the purpose of X-ray diffraction studies. See e.g., p. 288, right column, second paragraph. Crystals so generated are generally formed over longer periods of time, since the growth rate of the crystals is not important. Similarly, while crystal quality is important, yield is not. Therefore the resulting crystals tend to be of larger

dimensions, but smaller in amount. In contrast, the growth rate and yield of antibody or antibody fragment crystals, such as those of the present invention, which are generated on a large scale for purposes including therapeutic use, are very important. Consequently, such crystals are of smaller dimensions than those generated for X-ray diffraction studies. See the Table on page 6 of the specification.

The Examiner has cited no portion of Harris disclosing that Harris' antibody crystals would display the structural integrity and stability characteristics of the antibody and antibody fragment crystals of the present invention. In fact, the Examiner has conceded that Harris does not specifically teach that his crystal antibody is characterized by any  $\beta$ -sheet structural content or greater half-life *in vivo* than its soluble counterpart. See Office Action, page 5. And the Examiner has provided no scientific basis for his conclusion that Harris' antibody crystals would inherently possess the properties of the antibody or antibody fragment crystals of this invention. In the absence of such disclosure or scientific rationale, Harris' antibody crystals cannot be deemed to anticipate the antibody or antibody fragment crystals of the present invention. That being the

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case, Harris does not anticipate claims 5, 6, 9-11, 24-25, 31 and 33, which depend from claims 1-3 or claims 19-23 and, therefore, incorporate the elements thereof.

Claims 2, 4, 6, 11, 20-24 and 32 stand rejected under 35 U.S.C. § 102(b), as being "anticipated by" Hoedemaeker et al. (J. Biol. Chem. 1997; "Hoedemaeker"). According to the Examiner, Hoedemaeker discloses a single-chain Fv fragment of a monoclonal antibody and further provides a composition/formulation comprising the crystalline antibody fragment. The Examiner also asserts that the antibody fragment crystals of Hoedemaeker are inherently characterized by the properties of the antibodies of the present invention, i.e.,  $\beta$ -sheet structural content and/or increased half-life over its soluble content. Applicants disagree.

As in the case of Harris, Hoedemaeker's antibody fragment crystal was generated for the purpose of X-ray diffraction studies. Also, as in the case of Harris, the Examiner acknowledges that Hoedemaeker does not teach that his antibody fragment crystal is characterized by the features of  $\beta$ -sheet structural content, or greater half-life in vivo than its soluble counterpart, displayed by the antibody and antibody

fragment crystals of the present invention. Furthermore, the Examiner has pointed to no portion of Hoedemaeker suggesting that the Hoedemaeker crystals display the level of integrity and stability of the crystals of the instant application. And the Examiner has pointed to no scientific basis for his assertion that such characteristics of the antibody and antibody fragment crystals of the present invention would be inherent in Hoedemaeker's crystals. In the absence of such disclosure or scientific rationale, Hoedemaeker cannot anticipate claim 2, claims 20-23, or claims 6, 11, 24 or 32, which depend therefrom.

Claims 1, 5, 7, 11, 19-23, 31-34, 39 and 76 stand rejected under 35 U.S.C. § 102(b) as being "anticipated by" Margolin (WO 99/55310; "Margolin"). The Examiner states that Margolin discloses the generation of stabilized protein crystals including therapeutic proteins, such as antibodies, wherein the molecular weight of the protein can range from 600 daltons to 1000 kilodaltons, and compositions comprising such crystals and a polymeric carrier or at least one ingredient. The Examiner further asserts that Margolin's protein crystals include antibody crystals which appear to be the same as those of the present invention.

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Applicants have amended claims 1 and 19-23 to recite that the antibody or antibody fragment crystals of the present invention are characterized by  $\beta$ -sheet structural content. This feature was incorporated into those claims from claim 4. The Examiner did not reject claim 4 as being anticipated by Margolin. Accordingly, claims 1 and 19-23 are patentable over Margolin. So too are claims 5, 7, 31-34, 39 and 76, which depend from one or more of claims 1-3 and 19-23.

Claims 1, 3, 5, 17-18 and 70-71 stand rejected under 35 U.S.C. § 102(b) as being "anticipated by" Navia (U.S. Patent 5,849,296; "Navia"). The Examiner states that Navia discloses cross-linked crystals and teaches that these crystals include entire antibodies and antibody fragments. The Examiner further states that Navia teaches that the antibody crystal can be used in a diagnostic kit and that diagnostic antibodies can be used to detect targets *in vivo* and *in vitro*.

As amended, claims 1 and 3 specify that the antibody and antibody fragment crystals of the present invention are characterized by a particular  $\beta$ -sheet structure. This feature was incorporated into those claims from claim 4. The Examiner did not reject claim 4 as being anticipated by Navia.

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Accordingly, claims 1 and 3, as well as claims 5, 17 and 18, which depend therefrom, are patentable over Navia.

Claims 1, 5-11, 13, 15-16, 19-34, 39 and 76 stand rejected under 35 U.S.C. § 103, as being "unpatentable over" Margolin, as applied to claims 1, 5, 7, 11, 19-23 31-34, 39 and 76, and further in view of the Remicade package insert (August 1998; "Remicade"). Specifically, the Examiner asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce an Infliximab crystal in view of the teaching of Margolin.

As discussed above, claims 1 and 19-23 have been amended to incorporate the recital of claim 4. The Examiner did not reject claim 4 as being obvious over Margolin in combination with Remicade. Accordingly, claims 1 and 19-23 are patentable over Margolin. Claims 5-11, 13, 15-16, 24-34, 39 and 76 all depend from one or more of those amended claims. Accordingly, those claims are not obvious over Margolin in combination with Remicade.

Claims 43-68 and 74-45 stand rejected under 35 U.S.C. § 103 as being "unpatentable over" Harris, in combination with McPherson (Eur. J. Biochem, 1990; "McPherson") and further in

view of Pollock (J. Immunol. Methods 1999; "Pollock"). The Examiner asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the antibody crystallization conditions of Harris, in view of the teachings of McPherson. The Examiner also contends that, in view of Pollock, it would be *prima facie* obvious to use transgenic milk in processes based on such optimized crystallization conditions. Applicants disagree.

One of skill in the art seeking to carry out large-scale crystallization would not look to Harris or McPherson, because they relate to X-ray diffraction studies, which do not involve large-scale methods of crystallization. The Examiner's obviousness rejection, therefore, is based on no more than a reading of Harris and McPherson in hindsight of applicants' specification. Such a hindsight perspective cannot support the asserted obviousness of the present invention. Therefore, Harris, read in view of McPherson or Pollock, does not render obvious any of claims 43-68 and 74-75.

### Conclusion

Applicants have amended claims 1-3 and 19-23 to incorporate the features of canceled claim 4 to overcome the 35

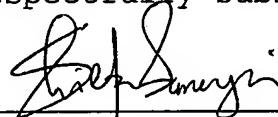
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U.S.C. § 102(b) rejections under Harris, Hoedemaeker, Margolin and Navia of claims 1-7, 9-11, 17-25, 31-34, 39, 70-71 and 76. The amendments also overcome the 35 U.S.C. § 103 rejections of claims 1, 5-11, 13, 15,-16, 19-34, 43-68 and 74-76, as discussed above. Added claims 80-83 incorporate features of claims 8, 13, 15 and 16, which were not subject to any § 102(b) rejection and which, for the reasons set forth above with respect to claims 1, 5-11, 13, 15-16, 19-34, 39 and 76, are not obvious in view of Margolin and Remicade. Accordingly, all of the claims are in condition for allowance.

Applicants request that the Examiner consider the foregoing amendments and remarks and pass this application to issue.

Respectfully submitted,



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